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INFLUENCE OF INJECTION PROTOCOL AND MEASUREMENT TECHNIQUE ON COMPUTED TOMOGRAPHIC ASSESSMENT OF GLOMERULAR FILTRATION RATE IN HEALTHY BEAGLE DOGS

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Influence of injection protocol and measurement technique on computed tomographic assessment of glomerular filtration rate in healthy Beagles

Computer Tomography (CT) allows investigation of glomerular filtration rate by assessment of contrast clearance.The purpose of this study was to compare the glomerular filtration rate (GFR) determined by three different contrast-medium injection techniques and four different measurement techniques in 9 dogs. In a randomized cross-over study, three different iohexol-injection protocols (700mgI/kg constant rate/700mgI/kg exponential decay rate/350mgI/kg constant rate) were administered during dynamic, whole renal volume scans and Patlak Plots originating from four different measurement techniques (standard transverse section(STST), optimized transverse section(OTST), dorsal reconstruction(DRT), and volume calculation techniques(VCT)) were compared. The measurement technique influenced the mean ± SD GFR results (STST, 2.49 ± 0.54 mL/kg/min; OTST, 2.72 ± 0.52 mL/kg/min; DRT, 3.00 ± 0.60 mL/kg/min, and VCT, 2.48 ± 0.51 mL/kg/min). The lower iodine dose resulted in a significantly higher GFR value (3.00 ± 0.65 mL/kg/min), compared with that achieved with higher dose administration (constant rate injection, 2.54 ± 0.45 mL/ kg/min and exponentially decelerated injection, 2.47 ± 0.48 mL/kg/min). The full dosage used for contrast CT studies reduced GFR compared to half dosage studies. This finding is important for patients with impaired renal function and for GFR measurement with CT-contrast medium protocols.

computed tomography, dog, glomerular filtration rate, contrast medium, iohexol

Mit der Computertomographie (CT) kann die glomeruläre Filtrationsrate (GFR) durch die Kontrastmittelausscheidung bestimmt werden. Das Ziel dieser Studie war es, die Bestimmung der GFR mit drei verschiedenen Kontrastmittel-Injektionstechniken und vier verschiedenen Messmethoden miteinander zu vergleichen. Für diese randomisierte Cross-over Studie wurden 9 gesunde Beagle-Hunde eingesetzt. Das Kontrastmittel Iohexol wurde in drei verschiedenen Protokollen appliziert (700mgI/kg konstant über 20s, 700mgI/kg exponentieller Abfall über 20s, 350mgI/kg konstant über 10s). Die vier Messmethoden (standard transversale Schnitt(STST)/ optimierte transversale Schnitt(OTST)/ dorsale Rekonstruktion(DRT/ Volumenkalkulationtechniken(VCT)) wurde bei allen CT-Scans und beiden Nieren durchgeführt und die GFR mit dem Patlak Plot berechnet. Die statistische Auswertung ergab, dass die die Messtechnik die GFR-Resultate beinflusste: (STST, 2.49 ± 0.54 mL/kg/min; OTST, 2.72 ± 0.52 mL/kg/min; DRT, 3.00 ± 0.60 mL/kg/min, and VCT, 2.48 ± 0.51 mL/kg/min). Zudem ergab die Injektion von 350mgI/kg signifikant höhere GFR-Werte (3.00 ± 0.65ml/kg/min), als die Injektion von 700mgI/kg (konstant: 2.54 ± 0.45ml/kg/min ($p<0.001$) und exponentiell: 2.47 ± 0.48ml/kg/min ($p<0.001$)). Diese Ergebnisse sind wichtig für Patienten mit einer reduzierten Nierenfunktion und für CT-GFR Messungen mit Kontrastmittel.

Computertomographie, Hund, Glomeruläre Filtrationsrate, Kontrastmittel, Iohexol

Influence of injection protocol and measurement technique on computed tomographic assessment of glomerular filtration rate in healthy Beagles

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OBJECTIVE
To compare values of CT-derived glomerular filtration rate (GFR) determined by 3 contrast-medium injection protocols and 4 measurement techniques in healthy Beagles.

ANIMALS
9 healthy Beagles (mean ± SD weight, 13.2 ± 1.6 kg).

PROCEDURES
Each dog underwent 3 iohexol-injection protocols (700 mg of iodine/kg administered at a constant rate over 20 seconds, 700 mg of iodine/kg administered following an exponentially decelerated injection over 20 seconds, and 350 mg of iodine/kg at a constant rate over 10 seconds) during dynamic, whole renal-volume CT in randomized order with an interval of ≥ 7 days between experiments. Values of GFR determined from Patlak plots derived by use of 4 measurement techniques (standard transverse section, optimized transverse section, dorsal reconstruction, and volume calculation techniques) were compared.

RESULTS
The measurement technique influenced the mean ± SD GFR results (standard transverse section technique, 2.49 ± 0.54 mL/kg/min; optimized transverse section technique, 2.72 ± 0.52 mL/kg/min; dorsal reconstruction technique, 3.00 ± 0.60 mL/kg/min, and volume calculation technique, 2.48 ± 0.51 mL/kg/min). The lower iodine dose resulted in a significantly higher GFR value (3.00 ± 0.65 mL/kg/min), compared with that achieved with either higher dose administration (constant rate injection, 2.54 ± 0.45 mL/kg/min and exponentially decelerated injection, 2.47 ± 0.48 mL/kg/min).

CONCLUSIONS AND CLINICAL RELEVANCE
In healthy Beagles, the CT-derived GFR measurements obtained after injection of a full dose of contrast medium were reduced, compared with measurements obtained after injection of a half dose. This finding is important with regard to potential nephrotoxicosis in dogs with impaired renal function and for GFR measurement with CT-contrast medium protocols. (*Am J Vet Res* 2018;79:1298–1305)

Glomerular filtration rate is an essential variable in evaluation of renal function. In dogs and cats, the determination of GFR with iohexol—an iodinated, water-soluble, nonionic, low-osmolar contrast medium—has become an accepted alternative to GFR determination with inulin and radioactive tracers.[1–7] Calculation of GFR from contrast-enhanced CT data correlates well with findings of more established methods such as renal scintigraphy and assessment of plasma iohexol clearance or the gold-standard inulin clearance.[8–10] Advantages of CT-GFR determination include the noninvasive measurement of contrast medium concentration in an ROI, possible morphological evaluation of the kidneys (eg, in cases of hydronephrosis, renal or ureteral calculi, and renal tumors) with good spatial resolution, and redundancy of blood or urine sample collection. The examination requires general anesthesia for immobilization of animals and exposes them to radiation.[9,11] In dogs, GFR determined from a single CT slice underestimates the actual GFR, compared with determinations made on the basis of renal scintigraphy and measurements of plasma iohexol clearance.[9,12] In pigs, single-slice CT-GFR correlates with inulin-derived GFR without bias for the right kidney and both kidneys.[8] Three-

ABBREVIATIONS

CL_{blood}	Whole blood iodine clearance
CL_{plasma}	Plasma iodine clearance
CRI	Constant rate injection
CT-GFR	CT-derived GFR
DRT	Dorsal reconstruction technique
EDI	Exponentially decelerated injection
GFR	Glomerular filtration rate
OTST	Optimized transverse section technique
ROI	Region of interest
STST	Standard transverse section technique
VCT	Volume calculation technique

phase whole-kidney CT with Patlak plot analysis underestimates right kidney GFR and total inulin-derived GFR.[13] In cats, a maximum difference between CT-GFR and GFR determined by plasma clearance testing or renal scintigraphy of up to 20% exceeds the definition of acceptable clinical use.[14]

The Patlak plot is a graphical representation of a 2-compartment mathematical model, which facilitates the calculation of CT-GFR by plotting the iodine content of each kidney for each measurement time point against the respective integrated iodine content of the aorta, both normalized to the respective iodine content in the aorta. The plot ideally becomes linear after the initial distribution phase, and the slope of the linear phase represents the whole blood clearance. Typical assessments of CT-GFR in animals use lower doses of contrast medium (150 to 350 mg of iodine/kg) than those used in routine contrast-enhanced abdominal CT examinations (700 mg of iodine/kg) and involve variable injection rates (CRIs between 0.25 and 4 mL/s). In people and dogs, the shape of the time-attenuation curve in the blood pool depends on the injection protocol. In most studies,[9,11,13,15–19] CT-GFR has been based on a single-slice technique, which includes both kidneys in 1 CT slice. It is recommended to exclude the main vessels and the renal hilus. In patients with pathological changes in the kidneys, it may be impossible for the operator to find an adequate, single image plane without including main vessels and the renal hilus under practical conditions.

To our knowledge, there are no published GFR studies regarding the influence of the injected dose of contrast medium, the injection protocol, or the measurement technique on time-dependent attenuation in the ROIs. The objective of the study reported here was to examine the influence of the injection protocol and measurement technique on CT assessment of GFR in healthy Beagles. To this end, the effect of 3 contrast medium injection protocols with 1 of 2 contrast medium doses (350 or 700 mg of iodine/kg) on the calculation of GFR determined from attenuation values of contrast-enhanced CT was investigated. In addition, 4 techniques (STST, OTST, DRT, and VCT) to measure attenuation within the kidneys were evaluated. The study was performed to test the null hypothesis of no differences in the determined GFR values among injection and measurement techniques.

Materials and Methods

Dogs

All procedures were approved by the Cantonal Veterinary Office of Zurich (license No: TVB 186/2012) and conducted in accordance with the guidelines established by the Animal Welfare Act of Switzerland. Nine healthy Beagles (4 sexually intact males and 5 sexually intact females) that weighed 9.5 to 14.8 kg (mean ± SD weight, 13.1 ± 1.6 kg) and were 2 to 3 years old were included in the study. The dogs were housed in standard kennels in groups of 2, 3, or 4 animals of the same sex at the university facility; were fed dry adult maintenance food; and had access to water ad libitum. All dogs were assessed as healthy on the basis of results of a physical examination, CBC, routine serum biochemical panel (blood urea concentration within the reference range of 7.4 to 12.6 mmol/L and creatinine concentration within the reference range of 98 to 163 mmol/L), urinalysis, and echocardiography performed by a board-certified veterinary cardiologist.

Anesthesia

Each dog underwent the same anesthetic protocol for each of the 3 experiments. Twenty minutes after IM premedication with acepromazine maleate[a] (0.03 mg/kg) and methadone hydrochloride[b] (0.5 mg/kg), anesthesia was induced by IV administration of propofol[c] (4 mg/kg) through a cephalic vein catheter by a board-certified veterinary anesthetist (TCG). Anesthesia was maintained with sevoflurane[d] in oxygen and air through an endotracheal tube by connection to a semiclosed circle system[e]; mechanical ventilation was provided throughout each experiment. To facilitate transient apnea, muscle relaxation was induced by IV administration of a bolus of rocuronium bromide[f] (0.3 mg/kg) administered 3 to 5 minutes before the start of the experiment. Respiration was maintained with mechanical ventilation with a tidal volume of 10 mL/kg and respiratory rate altered to maintain an end-tidal CO_2 concentration of 35 to 40 mm Hg. Anesthesia monitoring[e] included assessments of heart rate, respiratory rate, rectal temperature, peripheral oxygen saturation, arterial blood pressure (by a noninvasive method), inspiratory and expiratory oxygen concentration, end-tidal CO_2 concentration, and sevoflurane concentration. Prior to discontinuation of inhalation anesthesia and mechanical ventilation at the end of each experiment, each dog was examined to assess remnant muscle blockade with a train-of-four test; a minimum value of 90% was required prior to recovery. During recovery, control of blood pressure and heart rate continued. After recovery, monitoring included assessment (every 5 minutes) of rectal temperature, heart rate, and respiratory rate for another 30 minutes. The dogs were kept in a ward under routine observation for 12 hours until they were returned to their normal environment.

CT

During each experiment, CT assessment included an initial precontrast scan and 19 scans after start of the iodinated contrast medium[g] injection. The contrast medium administration was performed with an automatic programmable injector[h] through a cephalic vein catheter after completion of the precontrast scan. The entire volume of the kidneys was scanned repetitively at and after the start of injection at predetermined times as follows: 0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 2.50, 3.50, 4.50, 5.50, 6.50, 7.50, 8.50, 9.50, 10.50, 12.50, 14.50, and

16.50 minutes. The scans during the first 1.50-minute period were acquired during the first breath hold. Slowing the scan frequency allowed switching the ventilator on and off between the scans, in compliance with radiation safety principles.

Injection protocols

Each of the 9 dogs underwent all 3 injection protocols in random order (randomized by lottery tickets) with a minimal interval of 7 days between any 2 experiments. Two injection protocols included the full dose of contrast medium that is commonly used for abdominal CT in dogs (700 mg of iodine/kg); one injection was delivered at constant rate over a 20-second period (designated as 700-CRI), and the other was an EDI delivered over a 20-second period (designated as 700-EDI). The third protocol included half of the full dose (350 mg of iodine/kg) injected at constant rate over a 10-second period (designated as 350-CRI).

The EDI was performed as previously described.[20] Briefly, the injection followed an exponential decay curve formula of $y = a \times e^{-t/\tau} + b$, where y is the injection rate, b represents a final injection rate set at 0.63 mL/s, a + b is the initial injection rate set at 5 mL/s, e is a numeric constant equal to 2.718 (Euler number), t is the time after the start of injection (in seconds), and τ is an exponential decay constant set at 4 seconds. The injection was divided in 6 steps: 3 equal steps covered τ, and the other 3 steps were distributed equally over the remaining injection time.

The scanning settings of the CT unit[i] were as follows: 120 kVp; 250 mA; pitch, 0.688; rotation time, 0.75 seconds; and detector collimation, 16 × 0.75 mm. The raw data were reconstructed in 1-mm slices in a soft tissue algorithm with an increment of 0.5 mm and exported to an external workstation.

Measurement techniques

The CT images were reviewed by use of open-source imaging software[j] with a window level and width of 50 and 350 Hounsfield units, respectively, on a clinical work station[k] with 3 diagnostic screens.[l] One of the authors (MW) acquired the measurements under supervision of a board-certified veterinary radiologist (MD). Circular ROIs were generated to determine the attenuation value and SD deviation of the aorta at all time points by including as much of the aorta as possible but without including the margin to avoid volume averaging. For measurement of mean attenuation and SD from each kidney at all time points, the ROIs were drawn manually as large as possible with a closed polygon tool but excluded the renal margin to avoid volume averaging artifacts associated with inclusion of perirenal tissue in the voxel. Four measurement techniques (STST, OTST, DRT, and VCT) were evaluated.

For the STST, a single location including both kidneys and the aorta was defined in the transverse plane of acquisition, according to an established technique.[4] For the OTST, selection of the ROI location 1 or 2 slices caudal to each renal pelvis in the transverse plane of acquisition excluded the renal pelvis and main vessels. The ROI of the aorta was obtained in the STST. For the DRT, a multiplanar reconstruction was optimized for maximal inclusion of both kidneys in the image plane at a level dorsal to the renal pelvises, which allowed drawing of a dorsal ROI in each kidney that excluded the renal pelvises and main vessels. The ROI of the aorta was obtained in the STST. For the VRT, 10 ROIs were manually drawn for each kidney; 1 ROI each was drawn to include the cranial or caudal pole of the kidney, and 8 other ROIs were distributed evenly over the renal volume. The software generated the ROIs of the entire renal volume in the slices between the manually drawn ROIs automatically. The contours of the software-generated ROIs were reviewed and adjusted manually to the renal contours. Renal volumes for correction of the global clearance were conducted from the last scan of the STST. The ROI of the aorta was obtained in the STST **(Figure 1)**.

The values of all ROIs were exported to a commercial spreadsheet.[m] Subtraction of the precontrast attenuation value from each postcontrast value of renal and aortic attenuation generated the iodine content at each time point in each specific location. Adding up of the values from the columns to the left resulted in the area under the curve at each specific time point.

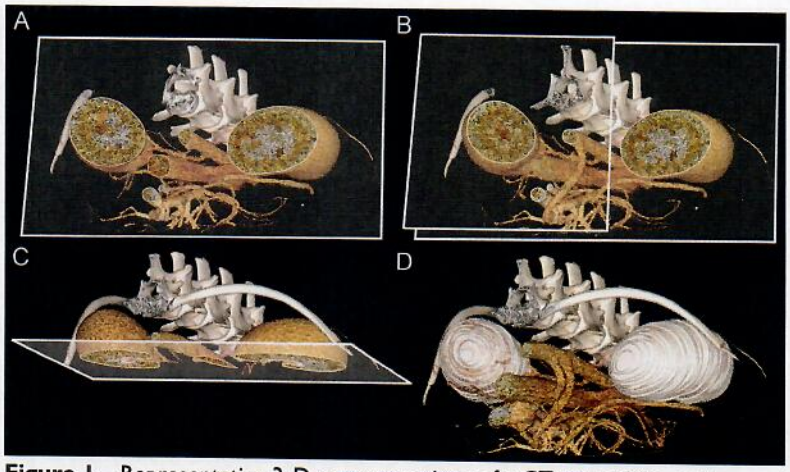

Figure 1—Representative 3-D reconstructions of a CT scan of the entire renal volume of a dog illustrating plane alignment for drawing the ROIs to perform 4 CT-GFR measurement techniques. A—For the STST, a single transverse plane includes parenchyma of both kidneys according to the established technique. B—By addition of a transverse plane in an optimal location in each kidney, the OTST is achieved. C—For the DRT, a scintigraphy-like plane is defined in a dorsal reconstruction to draw the ROI in the largest possible cross-sectional plane. D—The attenuation values of the entire renal volume (including renal parenchyma) generated in all transverse planes are incorporated in the VCT to obtain as much information as possible.

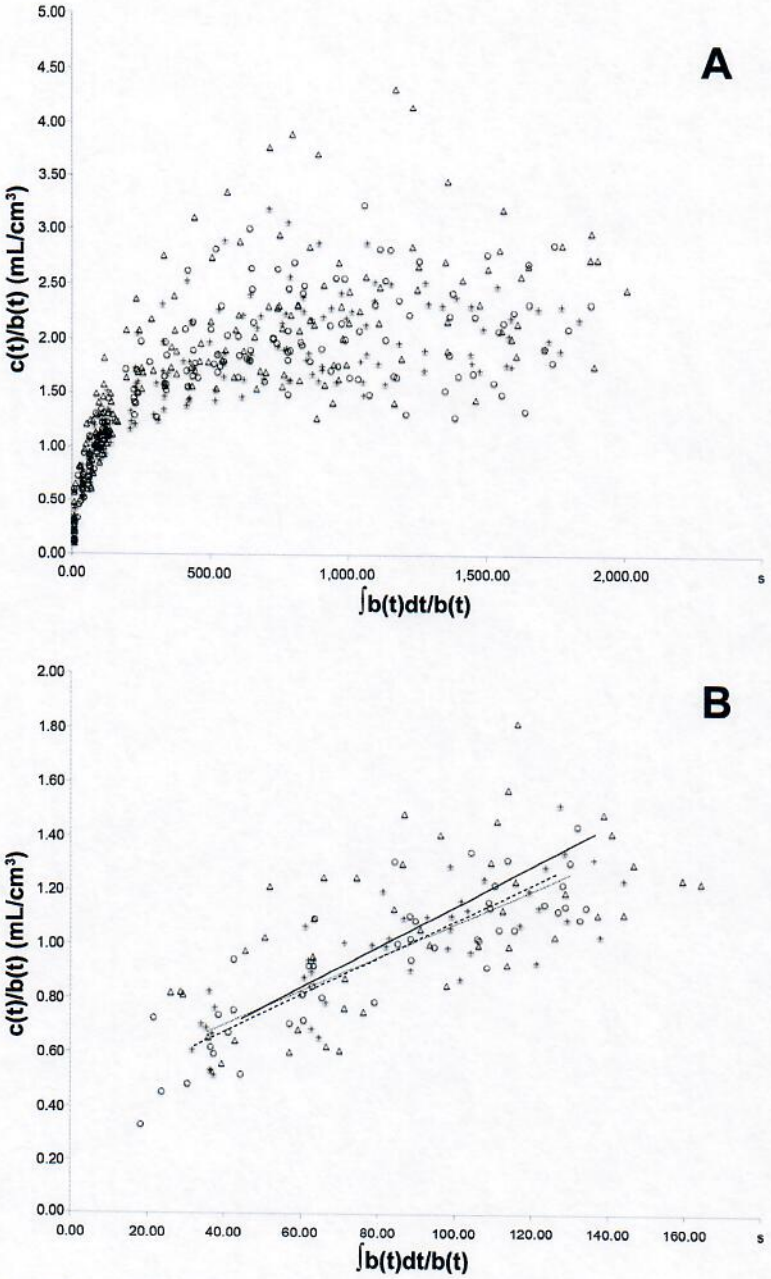

Figure 2—Patlak plots of renal iodine content at various times (c[t]) after injection of contrast medium against the respective integrated iodine content of the aorta (b[t]dt), both normalized to the respective iodine content in the aorta at time t (b[t]), for 9 healthy Beagles. In panel A, all measurements for all dogs from all time points are plotted; in panel B, all measurements for all dogs from 0.50 to 1.50 minutes after start of the contrast medium injection are plotted. The CT scans were acquired from the dogs by means of 3 injection protocols. Two injection protocols included the full dose of contrast medium that is commonly used for abdominal CT in dogs (700 mg of iodine/kg); one injection was delivered at constant rate over a 20-second period (designated as 700-CRI [circles]), and the other was an EDI delivered over a 20-second period (designated as 700-EDI [plus symbols]). The third protocol included half of the full dose (350 mg of iodine/kg) injected at a constant rate over a 10-second period (designated as 350-CRI [triangles]). The values acquired > 2.50 minutes after the start of injection were highly variable, and the regression curve was not linear. Linear regression analysis of the measurements between 0.50 and 1.50 minutes resulted in a steeper slope for data obtained following the 350-CRI (solid line), compared with the slopes for data obtained following the 700-CRI (stippled line) and 700-EDI (dashed line).

Patlak plots were generated by plotting c(t)/b(t) against ∫b(t)dt/b(t), with c(t) representing the iodine concentration in a volume of kidney tissue and b(t) depicting the blood iodine concentration at the time t. Patlak plots were drawn for all 19 time points and for the time points between the third and seventh scan (ie, 0.50 and 1.50 minutes). The linear regression through these 5 time points represented the CL_{blood} (mL of iodine/min/mL of kidney tissue). Multiplication of CL_{blood} by the plasma volume (1 – Hct) produced the CL_{plasma} (mL of iodine/min/mL of kidney tissue). The CL_{plasma} was then multiplied by the renal volume determined from the CT data. The sum of the values for the individual kidneys divided by body weight yielded CL_{plasma} corrected for body weight (mL/min/kg of body weight).

Statistical analysis

For statistical analysis, the results were exported to statistical software.[n] Descriptive statistics calculated included the mean, SD, median, and range. All values were tested for normal distribution with histograms, quantile-quantile plots, and Shapiro-Wilk test. The calculated GFR results originating from the various injection protocols and measurement techniques were compared with a Wilcoxon signed rank test for dependent variables; the level of significance was set at a value of $P < 0.05$. Outliers were defined as values that exceeded the upper and lower quartiles by 1.5 X interquartile range (25th to 75th percentile).

Results

In the Patlak plots including all 19 time points, linearity occurred between the third and seventh measurements (ie, between 0.50 and 1.50 minutes) in all kidneys, regardless of the injection and measurement techniques used. At later time points, the Patlak plots flattened for most data sets, with high variability among the dogs **(Figure 2)**. The mean linear regression of the data between 0.50 and 1.50 minutes was c(t)/b(t) = (0.002996 ± 0.00108) X ∫b(t)dt/b(t) + (0.847 ± 0.143), with the slope of the curve in units of 1/s and ∫b(t)dt/b(t) in seconds. The slope of the curve represented CL_{blood} (mL of iodine/min/mL of kidney tissue). Cor-

rection of CL_{blood} with Hct, kidney volumes, and body weight of the dogs resulted in the global GFR **(Table 1)**.

The data were normally distributed except for 1 sample (700-EDI with measurements obtained by OTST). Assessment of the data in groupings revealed an influence on the results of both injection protocol and measurement technique. Administration of the 700-CRI resulted in mean ± SD GFR of 2.54 ± 0.45 mL/min/kg. The GFR for the 700-EDI was 2.47 ± 0.48 mL/min/kg. Administration of the 350-CRI resulted in a GFR of 3.00 ± 0.65 mL/min/kg (Table 1). With regard to injection protocols, significant ($P < 0.001$) differences in GFR were evident between the 700-CRI and the 350-CRI and between the 350-CRI and the 700-EDI. The GFR determined following the 700-CRI and 700-EDI did not differ significantly ($P = 0.315$; **Figure 3**).

When data were examined on the basis of measurement technique, the STST resulted in a mean GFR of 2.49 ± 0.54 mL/min/kg. Use of the OTST for each kidney yielded a mean GFR of 2.72 ± 0.52 mL/min/kg. Values of GFR obtained by the DRT and VCT were 3.00 ± 0.60 mL/min/kg and 2.48 ± 0.51 mL/min/kg, respectively. The higher value of GFR obtained with the DRT was significantly ($P < 0.001$) different from values obtained by the other 3 measurement techniques (STST, OTST, and VCT). With the OTST, the GFR was significantly higher than that obtained by use of the STST ($P = 0.001$) or the VCT ($P < 0.001$). Measurement with the OTST generated results with the narrowest confidence interval. Among the data obtained by the OTST, there was a single outlier with a measured GFR of 4.10 mL/kg/min.

Overall, there were high interindividual differences in GFR values. Three samples did not fit into the range of 1.5 X the interquartile range and were classified as outliers (Figure 3). No complications were noted for the dogs during anesthesia and the postexperimental monitoring.

Discussion

On the basis of the data obtained from the dogs in the present study, the null hypothesis of there being no differences in the values of CT-GFR acquired with different injection protocols and measurement techniques had to be partially rejected. Significant differences in GFR between the 2 iodine doses were detected, whereas no difference was evident between injection methods (CRI and EDI). Administration of iohexol to provide a dose of 350 mg of iodine/kg generated significantly higher GFR than did administration of iohexol to provide a dose of 700 mg of iodine/kg.

Various canine CT-GFR studies have used iohexol at a dose of 300 mg of iodine/kg[9,15,16] or iopamidol at a dose of 150 mg of iodine/kg.[17] The results of the present study have suggested that

Table 1—Computed tomography–derived GFR data for 9 healthy Beagles determined by 3 contrast-medium injection protocols and 4 measurement techniques (STST, OTST, DRT, and VCT).

		GFR (mL/kg/min)				
Measurement technique	**Injection protocol**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
STST	700-CRI	2.4	0.37	2.28	2.06	3.19
	700-EDI	2.23	0.55	2.14	1.35	3.34
	350-CRI	2.83	0.55	2.95	1.99	3.62
OTST	700-CRI	2.56	0.46	2.40	2.05	3.41
	700-EDI	2.56	0.40	2.40	2.09	3.48
	350-CRI	3.03	0.59	2.82	2.13	4.10
DRT	700-CRI	2.83	0.44	2.79	2.33	3.85
	700-EDI	2.78	0.43	2.71	2.30	3.74
	350-CRI	3.39	0.73	3.37	2.16	4.32
VCT	700-CRI	2.37	0.43	2.22	1.88	3.26
	700-EDI	2.32	0.41	2.22	1.77	3.20
	350-CRI	2.75	0.60	2.60	1.88	3.69
Overall mean (SD)	—	2.67 (0.33)	0.5 (0.11)	2.58 (0.37)	2.00 (0.26)	3.6 (0.36)

Experiments were performed in a randomized order of injection protocols (3 times with an interval of at least 7 days between subsequent examinations) for each dog. Two injection protocols included the full dose of contrast medium that is commonly used for abdominal CT in dogs (700 mg of iodine/kg); one injection was delivered at constant rate over a 20-second period (designated as 700-CRI), and the other was an EDI delivered over a 20-second period (designated as 700-EDI). The third protocol included half of the full dose (350 mg of iodine/kg) injected at a constant rate over a 10-second period (designated as 350-CRI). The measurement techniques included a STST involving use of a single transverse plane as recommended in other studies. The OTST uses a second plane for optimal plane localization in each kidney. The DRT provides a scintigraphy-like view, and the VCT incorporates information for the entire volume.

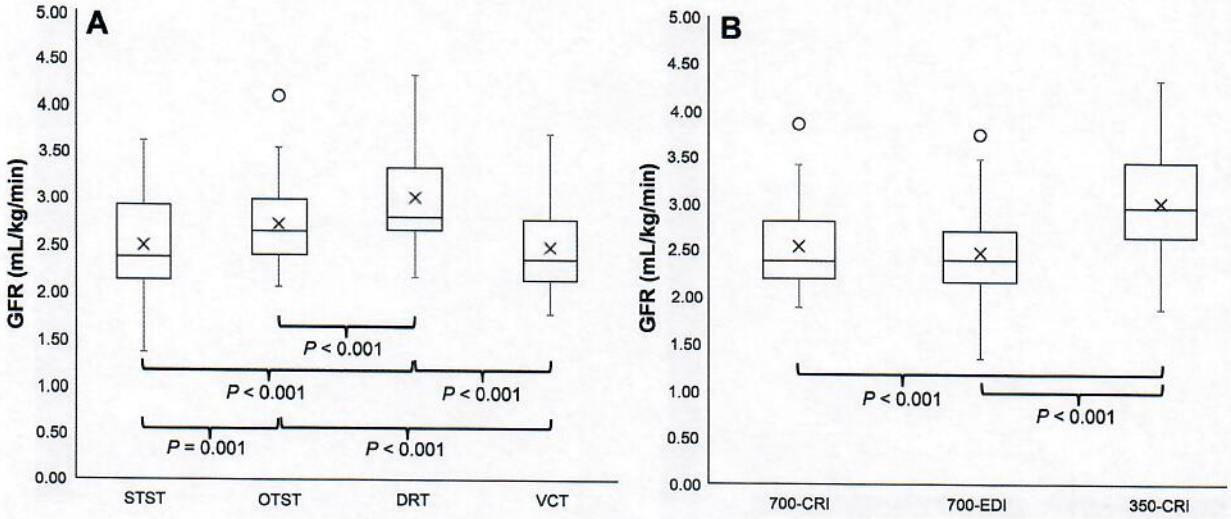

Figure 3—Box-and-whisker plots of CT-GFR data for 9 healthy Beagles determined by 3 contrast-medium injection protocols (700-CRI, 700-EDI, and 350-CRI) and 4 measurement techniques (STST, OTST, DRT, and VCT). Experiments were performed in a randomized order of injection protocols (3 times with an interval of at least 7 days between subsequent examinations) for each dog. Each box represents the interquartile range (25th to 75th percentile), the horizontal line in each box represents the median, the X represents the mean, and whiskers represent the range between the smallest and largest value within 1.5 X interquartile range. Circles represent outliers. A—Comparison of data by measurement technique. Mean GFR determined by the DRT was significantly different from values determined by the STST, OTST, or VCT. Mean GFR determined by the OTST was significantly different from values determined by the other 3 techniques. Data obtained with the OTST had the narrowest confidence interval. B—Comparison of data by injection protocol. Use of the 350-CRI resulted in significantly higher mean GFR than values obtained by use of either the 700-CRI or 700-EDI. The GFR determined by use of the 700-CRI or 700-EDI did not differ significantly. The statistical outliers for the 700 CRI (3.85 mL/min/kg) and 700-EDI (3.74 mL/min/kg) were the same dog. ***See*** Figure 2 for key.

higher doses of contrast medium temporarily impair renal function and lead to lower GFR. Possible mechanisms for this finding include direct nephrotoxic effects on tubule cells as well as ischemia mediated by decreased availability of nitric oxide and generation of reactive oxygen species particularly in the medulla of the kidney. Contrast media are still considered safe but can precipitate and cause acute kidney injury in a small number of high-risk patients.[1,21,21-25]

The values of CT-GFR obtained in the present study are in agreement with published mean ± SD CT-GFR values for healthy dogs, which include 1.84 ± 0.80 mL/min/kg,[17] 2.57 ± 0.33 mL/min/kg,[9] 2.91 ± 0.60 mL/min/kg,[2] and 4.21 ± 0.25 mL/min/kg.[16] One study[15] measured CT-GFR from the right kidney only in 17 dogs, and results ranged from 2.04 ± 0.36 mL/min/kg to 2.14 ± 0.43 mL/min/kg, which would indicate a total GFR of approximately 4 mL/min/kg. Glomerular filtration rate values depend on patient characteristics. Grouping healthy dogs into 4 weight categories of 1.8 to 12.4 kg, 13.2 to 25.5 kg, 25.7 to 31.6 kg, or 32 to 70.3 kg resulted in GFR values (mean ± SD) of 3.7 ± 0.5 mL/min/kg, 3.0 ± 0.5 mL/min/kg, 2.5 ± 0.4 mL/min/kg, and 2.4 ± 0.6 mL/min/kg, respectively.[26] A study[16] with a similar design as that of the present study resulted in values of approximately 4.4 mL/min/kg. The low threshold reference values for GFR measured with renal nuclear medicine techniques in dogs were set at 3 mL/min/kg.[27]

For the description of the Patlak plots beyond usual scan duration, all dogs were scanned at defined time points from the start of the contrast medium injection to 16.50 minutes after injection. Results of the present study indicated an absence of linearity over the measured 16.50-minute period in the Patlak plot analysis with flattening of the slope of the linear regression curve. Appropriate choice of included measurements is essential because the slope of the linear regression curve represents whole blood clearance. The 2-compartment model representing the theoretical basis of Patlak analysis does not incorporate the fact that the tracer leaves the renal compartment and enters the renal pelvises. Depending on plane location, accumulation of large amounts of contrast medium potentially deteriorates image quality. Linearity of the values of the Patlak plot in the present study occurred between 0.50 and 1.50 minutes after injection of contrast medium, and deterioration of the distribution occurred at 2.50 minutes. After iohexol injection in another study,[16] an initial peak of renal parenchymal enhancement was detected at 15 to 21 seconds and peak aortic enhancement was detected between 9.5 and 16 seconds with a subsequent lower peak at detected at 25 to 36 seconds, which is in agreement with the results of the present study. That other study[16] involved scan durations of 120 seconds and generated linear plots in agreement with findings of other investigations[8,9,12,15-17] that involved scan durations of up to 150 seconds. Taken together, these results suggest that inclusion of late measurements leads to incorrectly low GFR values.

The STST used in the present study corresponded to the technique that was compared with renal scintigraphy and the gold-standard inulin clearance in a previous study.[9] The newly introduced measurement technique, DRT (a scintigraphy-like dorsal reconstruction), generated significantly higher GFR results, compared with results for the other 3 techniques. The OTST, a new optimized technique based on the accepted standard technique, generated the highest GFR values with the narrowest confidence interval in the present study. The STST involving both kidneys in the same transverse plane resulted in partial inclusion of 1 hilar area in the images for reasons of anatomic localization even though the renal pelvis should be avoided when drawing the ROI. For the OTST, placement of 2 independent planes excluded the renal hilus and resulted in a minor, significant increase in GFR values as well as reduction of the confidence interval. The results of the present study suggested that the OTST is more exact and is the preferred measurement technique if a set of volume scans is available. In kidneys with an abnormal structure, application of the more time-consuming VCT allows active exclusion of renal masses or large cysts. The use of single-plane measurement techniques in humans who have kidneys with abnormal anatomic morphology can potentially lead to higher results for GFR (inclusion of a mass or cyst in the renal volume) or to lower values for GFR (inclusion of a mass or cyst in the ROI).[28] If the data for the volume calculation do not originate from a biphasic contrast study, the patient receives a higher radiation exposure because of repetitive volume acquisition, compared with the exposure associated with the STST.

With regard to the anesthetic protocol used in most published studies of GFR evaluation in dogs, anesthesia induced with propofol and maintained with isoflurane in air and oxygen is most typical. Dogs that received no premedication before induction of anesthesia with propofol had slightly higher CT-GFR values (2.53 ± 0.33 mL/min/kg[9] and 4.21 ± 0.25 mL/min/kg[16]), compared with dogs that were premedicated with SC administration of 0.2 mg of butorphanol/kg (1.84 ± 0.80 mL/min/kg[17]). In the present study, the dogs were premedicated with acepromazine (0.03 mg/kg, IM) and methadone (0.5 mg/kg, IM) consistent with a routine protocol at our clinic. Acepromazine is an antagonist at α_1-adrenoreceptors and can therefore lead to peripheral vasodilatation, decreased cardiac output, and potentially decreased arterial blood pressure. Opioids, such as methadone, can result in bradycardia. In healthy animals, the premedication used in the present study should not cause a clinically relevant hypotension.[29] A recent study[15] assessed various anesthetic agents and CT-GFR measurements obtained by the use of dynamic CT in dogs. Results indicated that etomidate, propofol, or thiopental in combination with isoflurane inhalation anesthesia did not adversely affect GFR measurements (2.14 ± 0.43 mL/min/kg, 2.06 ± 0.29 mL/min/kg, and 2.04 ± 0.36 mL/min/kg, respectively).[15] Therefore, results of the present study were unlikely to have been affected by the anesthetic protocol used.

In human medicine, it has been shown that CT-GFR determination can be integrated in routine abdominal CT with acquisition of a precontrast and 2 or 3 postcontrast scans to provide additional information about renal function.[28] The results of the present study suggested that optimal timing after contrast medium injection for data acquisition is at 0.5 minutes for the first measurement and before 2.50 minutes for the second measurement required for the Patlak plot analysis. The OTST allowed exclusion of the renal hilus and provided data with the narrowest confidence interval. The doses of contrast medium used in the present study pose a source of conflict between the requirements of the routine evaluation and the impact of the contrast medium on the results of GFR determination. If the main focus of an evaluation of a dog is the determination of GFR based on volume data, it is recommended to administer an IV injection of 350 mg of iodine/kg over a 10-second period; acquire 3 scans at 0.5, 1.0, and 1.5 minutes after the start of the injection; and use the OTST. A distribution of the scans over an interval of > 2.0 minutes could be considered depending on the breath-holding abilities of the patient.[16]

The lack of use of a gold-standard technique, optimally repeated after data collection by means of the other techniques, represented a limitation of the present study. Determination of GFR by means of CT is well established, and administration of contrast media is considered extremely safe.[9,23] The randomized order in which the dogs underwent the 3 iohexol-injection protocols without reduction of the GFR values over the study duration minimized the risk of experimental error, but the study population was small. Future studies to investigate the approximation of CT-GFR values to measurements obtained by other means along with reduction of the contrast medium dose are warranted.

In CT-GFR assessments, temporary nephrotoxic effects of the contrast medium injection have to be considered, especially in patients with impaired renal function. Overall, the hypothesis of the present study had to be partially rejected. Among the study dogs, administration of the 700-CRI or 700-EDI resulted in significantly lower GFR values, compared with that obtained with the 350-CRI. The different measurement techniques resulted in variable results with significant differences between the GFR values obtained by the DRT and all other techniques and between the GFR values obtained by the OTST and VCT. Nevertheless, the results of the present study suggested that the OTST generates data with the narrowest confidence interval. In kidneys with regional alteration of filtration, the VCT could represent an interesting alternate measurement technique. For daily clinical practice, it is advisable to set a standard protocol for CT-GFR measurement in dogs.

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Footnotes

a. Prequillan, Arovet AG, Dietikon, Switzerland.
b. Methadon Streuli, 10 mg/mL, Streuli Pharma, Uznach, Switzerland.
c. Propofol 1%, Fresenius Kabi AG, Stans, Switzerland.
d. Sevoflurane, Baxter AG, Volketswil, Switzerland.
e. Datex Ohmeda S5 Avance, Soma Technology Inc, Bloomfield, Conn.
f. Esmeron, MSD AG, Luzern, Switzerland.
g. Accupaque 350, 350 mg of I/mL, GE Healthcare, Glattbrugg, Switzerland.
h. Accutron CT-D Medtron Injector, SMD Medical Trade GmbH, Salenstein, Switzerland.
i. Brilliance CT 16-slice, Philips AG, Zurich, Switzerland.
j. OsiriX Imaging Software, version 4.1, 64-bit, Geneva, Switzerland.
k. MacMini (2010) 2.4 GHz Intel Core Duo, Apple Switzerland AG, Zurich, Switzerland.
l. EIZO MX210 (1,600 X 1,200) 21.5 in, EIZO AG, Wädenswil, Switzerland.
m. Microsoft Office Excel for Mac, Microsoft Schweiz GmbH, Wallisellen, Switzerland.
n. SPSS, IBM SPSS Statistics, IBM Schweiz AG, Zurich, Switzerland.

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